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Subgenual Cingulate Cortex Activity in Predicting Risk Factor and Treatment-Response in Depression

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Abstract

Major depressive disorder (MDD) contributes significantly to morbidity, disability, and decreased quality of life, despite the expansion of treatment options. This, in part, is caused by a lack of valid, applicable, and reliable biomarkers to predict the risk, treatment response, and prognosis of depression. In recent years, the anterior cingulate cortex, in particular pars subgenual (sgACC), has received much attention due to its potential utilization as a neural endophenotype for depression. This essay discusses the functional activity of sgACC, mostly by functional magnetic resonance imaging, in relation to predicting risk for developing depression, predicting patient response-to-treatment, and eventually, to creating a platform for the personalized psychiatric approach to each patient. The caveats and conditions need to be met are also discussed, in order to firmly establish sgACC activity as a valid biomarker for depression.

Keywords: depression, anterior cingulate cortex, subgenual, biomarker, fMRI

Abstrak

Walaupun teknologi kedokteran berkembang amat pesat, gangguan depresi mayor masih merupakan salah satu penyebab utama terjadinya morbiditas, disabilitas, dan penurunan kualitas hidup. Hal ini disebabkan salah satunya karena belum ada penanda biologi yang valid dan reliabel yang dapat diaplikasikan untuk meramalkan risiko terjadinya depresi pada populasi, sekaligus untuk memprediksi respons terhadap terapi dan prognosinya. Korteks singulatus anterior pars subgenual (sgACC) saat ini sedang diteliti secara intensif karena potensinya untuk bertindak sebagai endofenotip untuk depresi. Tulisan ini akan membahas aktivitas fungsional sgACC yang diukur terutama dengan fMRI--dalam peranannya untuk memprediksi risiko, respons, dan prognosis depresi. Hal ini dapat dijadikan dasar sebagai pendekatan personal untuk tiap pasien depresi. Selanjutnya, akan dibahas juga tentang kelemahan dan tantangan yang dihadapi sebelum menetapkan sgACC sebagai penanda biologi rutin untuk depresi.

Kata Kunci: depresi, anterior cingulate cortex, subgenual, biomarker, fMRI

INTRODUCTION

Major depressive disorder (MDD) is one of the leading causes of years lived with disability, with a high relapse rate and lifetime prevalence of 15% ⁽¹⁾. Socioeconomically, it is a costly and socially impair-

ing disorder ⁽²⁾. In clinics, MDD diagnosis is generally made based on the DSM-V ⁽³⁾. There have to be at least five of nine criteria of depressive symptoms, including sadness, anhedonia, and somatic disturbances, with a duration longer than 2 weeks. There

are many treatments available for depression, ranging from cognitive behavioral therapy to antidepressant drugs with various mechanisms. However, despite the extensive, rapidly-expanding development in psychopharmacology, up to one-third patients continued to have persistent symptoms even after a full course of treatment ⁽⁴⁾. This happens because, at least in part, the therapy for depression is chosen empirically based on clinical presentation, which actually consists of a spectrum with no distinctive line between subtypes ⁽⁵⁾. A therapy for depression, as well as for other medical conditions, ideally must be adjusted individually, since every patient has their unique phenotype, resulting from variability in genetic predisposition to environmental factors ⁽⁶⁾.

In this context, identifying a biomarker would be beneficial. A biomarker could provide clear and distinctive insight into diagnosis, risk factors, or prognostic response to a therapy ⁽⁷⁾. It would be even more beneficial if the biomarker itself is involved in the pathological pathway because clinicians would be able to administer a targeted-therapy rather than the empirical ones. By identifying biomarkers in depression, a more individualised therapy can be assigned, which eventually would increase the success rate of the treatment. ^(8,9)

The difficulty in finding a suitable candidate for depression biomarker is its complexity in term of the pathogenesis. Depression is multifactorial, where extensive interactions take place in the neural circuitry ⁽¹⁰⁾. Another caveat is the difficulty to detect subclinical cases, which is partially due to mental-health illiteracy of the society in seeking help for treating the mental disorders, besides because the diagnosis of MDD often requires clear and full-blown

symptoms that increases the threshold of clinical detection ⁽¹¹⁾. When a patient presents with full-spectrum symptoms, the opportunity to spot any subclinical biomarker to predict population-at-risk would then be missed.

After its introduction, about two decades ago, the utilization of functional magnetic resonance imaging (fMRI) has become numerous both in clinical and research setting. The use of fMRI in depicting brain activity provides a better insight into the pathogenesis of depression in a dynamic way, and potentially, could serve as a reliable biomarker. Subgenual anterior cingulate cortex (sgACC) is a part of the cingulate cortex below the genu of corpus callosum (hence the name, subgenual). Early lesion studies in animals ^(12, 13) suggested that sgACC is associated with the modulation of emotional behavior. Case-controlled structural neuroimaging in human studies have found a significant reduction in the grey matter volume of the anterior cingulate cortex among MDD patients ^(14, 15, but see 16). However, it has to be noted that psychiatric disorders, including depression, are multifactorial; they occur because of gene-environment interaction in each individual ⁽⁶⁾. Therefore, it would be more reasonable to search for *functional* biomarker rather than *structural*, since functional biomarkers are arguably more representative in reflecting the complex interaction of environment, neural endophenotypes, and genetic traits.

Despite criticisms around fMRI utilization, it has been enabling clinicians and researchers to acquire the impression of local field potential within any particular region of the brain ^(17, 18). In identifying the sgACC activity described above, fMRI is more superior to other neuroimaging tech-

niques, such as electroencephalography in terms of spatial resolution, and positron emitting tomography (PET) in terms of invasiveness and safety. This superiority posits fMRI as a state-of-the-art modality in cognitive neuroscience today, evidenced by the abundance of fMRI-based research publications. However, when interpreting fMRI findings, it should be noted that fMRI does not display the direct neural activity. Rather, it reflects the vascular dynamic in response to local field potentiation within a certain area of the brain ⁽¹⁷⁾.

This essay focuses on the functional activity of sgACC in ⁽¹⁾ predicting the risk factor of developing depression, and ⁽²⁾ predicting the treatment response.

In line with studies about volumetric change in sgACC ⁽¹⁹⁾, association between the functional activity and the risk of suffering depression in adolescence has also been shown. Masten, et al. ⁽²⁰⁾ in a small-sampled cohort study (N=20, mean age=13) examined the relationship between sgACC activity during ostensible peer rejection (using a computer simulation) and the level of depressive symptoms during the following year. They found that greater sgACC activity elicited during the simulation was associated with increases of depressive symptoms at follow-up examination. This study has elegantly summed up the interaction between negative environmental stimuli (peer rejection) and an endophenotype (sgACC blood oxygen level-dependent [BOLD] increase) in increasing the risk of depression. The small sample size, however, limited its power and generalisability in larger population.

The heritability nature of depression has been well known ⁽¹⁰⁾. Gotlib, et al. ⁽²¹⁾ conducted an experiment using a reward-or-punish game simulation involving 13 nev-

er-disordered daughters of mothers with history of recurrent depression and 13 age-matched control subjects. They found that, when punishment was given, the subjects with familial history of depression had greater activation in the ACC than the control group. This study reinforces the crucial role of ACC activity when faced with negative environmental stressor and associates it with the risk factor of developing depression, as well as confirming the heritability of depression by identifying a potential endophenotype.

The study about the importance of functional sgACC activity in identifying at-risk population is still ongoing. Methodological and conceptual considerations have to be taken into account before the integration of these findings into clinical settings ⁽²²⁾.

In terms of predicting the response to treatment, the original notion originated from positron-emitting tomography (PET) study ⁽²³⁾. Due to the invasiveness and the risk of PET, there was a shift of functional neuroimaging study toward fMRI-based research.

To date, across numbers of studies, the increasing in sgACC activity has been associated with good outcome when treated with pharmacological antidepressants, regardless of the kind of drugs used. For example, Samson, et al. ⁽²⁴⁾ examined the activity of sgACC in predicting treatment response to mirtazapine or venlafaxine. A pre-treatment greater activation in the cingulate cortex predicted the greater clinical response to the drugs studied. Other research revealed similar results, that ACC activity serves as a strongest predictive value in predicting treatment response to citalopram—another type of antidepressant ⁽²⁵⁾, and to fluoxetine, the most common antide-

pressant prescribed ⁽²⁶⁾. Consistently, these studies demonstrate that patients with greater functional activation of anterior cingulate cortex would have faster improvement with pharmacological antidepressant. Most of them drew on their conclusion from a small sample ($N = 17$ to 20 patients with balanced control), but given the observed consistency and high replicability, this finding can potentially be utilised to establish a clinical biomarker.

A meta-analysis did confirm the findings and suggested that ACC activity and hippocampal volume have potential significance to be developed into a prognostic marker in depression treatment ⁽²⁷⁾. However, the authors only considered standard psychotherapy and pharmacotherapy in their inclusion criteria, thus, excluding the possibility of ACC prediction of treatment response in other therapies, such as deep-brain stimulation, transcranial magnetic stimulation, as well as augmentation of drug with cognitive behavior therapy ⁽²⁸⁾.

Interestingly, a number of studies reported that a decrease in sgACC activity correlated with a better outcome if treated with psychotherapy (such as cognitive behavior therapy, CBT) rather than pharmacologic antidepressant. Siegle, Carter ⁽²⁹⁾ prospectively studied 14 medication-free subjects with depression who were about to undergo CBT. They found that those with hypoactive sgACC (Brodmann's area 25) would respond better to CBT. A notion should be made that this group used a higher-power fMRI scanner (3 Tesla). Fu, et al. ⁽³⁰⁾ failed to replicate their findings when using 1.5 Tesla scanner. Instead, they found the correlation in dorsal anterior cingulate rather than sgACC. A similar study with PET ⁽³¹⁾, on the other hand, was consistent

with the finding by Siegle and colleagues, supporting that hypoactivity of sgACC, rather than dorsal ACC is more likely to be associated with better response to CBT.

More recently, Argyelan et al. ⁽³²⁾ observed that electroconvulsive therapy (ECT) can have an antidepressant effect, which can be predicted by SCC relative underactivity. Richey, et al. ⁽³³⁾ also examined the effectiveness of CBT in patients with depression ($N=22$) based on their neural activity, focusing on the ventral and dorsal prefrontal cortex. Intriguingly, they found the opposite effect, in which hyperactivity, rather than hypoactivity, observed in the ventromedial prefrontal cortex is predictive to the success of subsequent CBT. This inconsistency—not only in this case, but also across fMRI publications—can be due to differences in the region of interest (ROI), baseline calibration of the apparatus, voxel clustering, and the choosing of statistical threshold ^(34, 35). Most of the studies involved small sample group, therefore, limited their power and generalisability ^(27, 34). Interestingly, using whole-genome expression analysis, Barthas, et al. ⁽³⁶⁾ have discovered a particular molecule called mitogen-activated protein kinase phosphatase -1 which is epigenetically upregulated in a cingulate area during depression in an animal model. This, together with the clinical findings, reinforced the pivotal role of the cingulate in depression pathogenesis.

SUMMARY

In summary, the hyperactivity of sgACC can be a potential biomarker to predict the risk of individuals suffering from depression. By identifying those who are at risk of developing psychiatric disorders, actions could be made to prevent educational failure and socio-economical compli-

cations, or in other words, allowing further step in providing mental-health assistance to be taken⁽³⁷⁾. The workup with the Clinical Staging Model developed by Hickie, et al.⁽³⁸⁾ would also be benefited by the introduction of biomarkers, especially in identifying those who have risk factors for depression, where sgACC could serve as a likely candidate.

In terms of predicting treatment response, the distinction between medication-responsive and psychotherapy-responsive also could be drawn based on sgACC activity, although further research is still needed. This unique property of sgACC functional activity could encourage the division of depressive disorders based on their potential response to treatment. Once established, clinicians will have a pre-treatment guide to start medication, which is much better than doing trial-and-error and watchful waiting for weeks before deciding to switch or modify the therapy⁽³⁹⁾. However, learning from previous quests for biomarkers, a standardized examination and interpretation should be made prior to its application in clinical setting to prevent false-positive findings⁽⁴⁰⁾.

Finally, there has been also a concern that a predictive biomarker should be able to show accuracy in individual level⁽²⁷⁾. Certainly, further research in this area is mandatory, involving larger samples and more standardized protocol as well as statistical methods. A very good lesson can be taken from genomic biomarkers, where a guideline for assessing clinical significance has been developed⁽⁴¹⁾. The translation of statistical significance to clinical significance would be necessary, especially in predicting the prognostic value, because virtually all fMRI studies can only report the statistical significance.

To increase the specificity and sensitivity to a diagnosis, a combination of two potential biomarkers can also be considered. For example, by combining a neuroimaging biomarker with some neuropsychological portraits⁽⁴²⁾ or by combining multiple neuroimaging biomarkers⁽⁴³⁾.

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